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**A randomized controlled trial of pharmacist-led therapeutic carbohydrate and energy restriction in type 2 diabetes**

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Abstract (Word Count 150)

Type 2 diabetes can be treated, and sometimes reversed, with dietary interventions; however, strategies to implement these interventions while addressing medication changes are lacking. We conducted a 12-week pragmatic, community-based parallel-group randomized controlled trial (ClinicalTrials.gov: NCT03181165) evaluating the effect of a low-carbohydrate (<50g), energy-restricted diet (~850-1100 kcal/day; Pharm-TCR; n=98) compared to treatment-as-usual (TAU; n=90), delivered by community pharmacists, on glucose-lowering medication use, cardiometabolic health, and health-related quality of life. The Pharm-TCR intervention was effective in reducing the need for glucose-lowering medications through complete discontinuation of medications (35.7%; n=35 vs. 0%; n=0 in TAU;  $p<0.0001$ ) and reduced medication effect score compared to TAU. These reductions occurred concurrently with clinically meaningful improvements in hemoglobin A1C, anthropometrics, blood pressure, and triglycerides (all  $p<0.0001$ ). These data indicate community pharmacists are a viable and innovative option for implementing short-term nutritional interventions for people with type 2 diabetes, particularly when medication management is a safety concern.

## Introduction

Type 2 diabetes is typically considered a chronic progressive disease, but it is now established that reversal/remission of type 2 diabetes is possible. Targeted nutritional approaches have garnered attention due to the increasing evidence base suggesting they can be used to induce type 2 diabetes reversal/remission<sup>1-3</sup>. In a non-randomized trial, continuous remote-care using a very low-carbohydrate, high-fat, ketogenic diet led to substantial weight loss, lowered haemoglobin A1C (HbA1c), and reduced need for glucose-lowering medications (including insulin) in a diverse group of 262 patients with type 2 diabetes<sup>4-6</sup>. In a cluster randomized controlled trial (RCT), Lean and colleagues<sup>7</sup> showed that a 12-week very low-calorie (~850 kcal day) total diet replacement method followed by food reintroduction resulted in remission of type 2 diabetes (sub-diabetes HbA1c and taking no glucose-lowering medications) in 46% of newly diagnosed patients at one year follow-up. Online self-management interventions also report reduced oral diabetes medications and insulin dose, while lowering HbA1c, in participants with type 2 diabetes<sup>8</sup>. The idea that diet therapy could reduce or eliminate the need for glucose-lowering medications is intriguing but raises several important issues in diabetes care, including 1) how to limit the risk of hypoglycemia due to contemporaneous over-medication; and 2) the lack of guidance and/or knowledge of how to safely manage medication reductions when patients follow very low-carbohydrate or low-calorie diets.

While physicians are typically at the centre of diabetes care, pharmacists are more accessible and patients with type 2 diabetes make more annual visits to their pharmacist than primary care physician; this is especially true in rural areas<sup>9</sup>. Community pharmacists have expertise in medication management and can serve an important role in overall diabetes management<sup>10</sup>. Due to the need to reduce or eliminate glucose-lowering medications when type 2 diabetes patients

follow a very low-carbohydrate or low-calorie diet<sup>4,7,11</sup>, community pharmacists may be ideally positioned to safely and effectively deliver nutrition interventions targeted at reducing diabetes medication use and promoting type 2 diabetes remission. Accordingly, the aim of the Pharmacist-led therapeutic carbohydrate restriction (Pharm-TCR) as a treatment strategy for type 2 diabetes trial<sup>12</sup> was to determine if a very low-carbohydrate, low-calorie diet - led by community pharmacists - could reduce the need for glucose-lowering medications and facilitate improvements in cardiometabolic health when compared to guideline-based treatment-as-usual (TAU).

## Results

### Baseline characteristics of study participants

Between July 7<sup>th</sup> 2017 and April 1<sup>st</sup> 2019, we recruited 188 individuals from 12 pharmacies across southern British Columbia, Canada. Sample size fell just short of the target recruitment of 100 per group; 98 participants randomized to the Pharm-TCR group and 90 participants randomized to the TAU group comprised the intention-to-treat population. Four participants in the Pharm-TCR group and 15 participants in the TAU group dropped out prior to commencing the trial. Furthermore, 16 participants in the Pharm-TCR group and 15 participants in the TAU group dropped out after commencing the trial. Sex assignment was missing for 13 participants. The CONSORT Flow Diagram is shown in Figure 1. Baseline participant characteristics are reported in Table 1.

Table 1: Baseline characteristics

	Pharm-TCR	TAU
Sex		
Male (%)	44	43
Female (%)	56	57
Age (years)	58 (11)	59 (8)
T2D Duration (years)	11.8 (8.0)	8.8 (8.0)
Body weight (kg)	102.3 (21.6)	103.4 (19.7)
BMI (kg/m <sup>2</sup> )	36.0 (6.0)	35.1 (5.3)
Waist Circumference (cm)	115.6 (13.6)	115.8 (16.3)
Body Fat %	39.0 (6.3)	40.2 (6.3)
Systolic Blood Pressure (mmHg)	138 (17)	136 (16)
Diastolic Blood Pressure (mmHg)	80 (14)	82 (13)
HbA1c (%; percentage points)	7.9 (1.5)	7.8 (1.4)
HbA1c (mmol/mol)	63 (16)	61 (15)
Fasting Glucose (mmol/L)	9.3 (3.2)	9.3 (3.1)
GGT (mmol/L)	40.8 (39.6)	47.8 (42.6)
AST (mmol/L)	24.1 (13.9)	31.1 (21.5)
ALT (mmol/L)	31.3 (20.0)	42.8 (30.5)
HDL Cholesterol (mmol/L)	1.21 (0.32)	1.21 (0.31)
LDL Cholesterol (mmol/L)	2.38 (0.95)	2.49 (0.98)
Total Cholesterol (mmol/L)	4.46 (1.15)	4.56 (1.13)
Triglycerides (mmol/L)	1.97 (1.47)	2.0 (1.02)
CRP (mmol/L)	5.1 (5.3)	5.5 (5.1)
Medication Effect Score	2.1 (1.7)	1.8 (1.7)
Leisure Score Index	22.2 (26.7)	23.7 (21.7)
Health Related Quality of Life		
Physical Functioning	70.1 (28.8)	69.6 (28.2)
Role Functioning	71.9 (39.1)	71.7 (40.7)
Social Functioning	81.3 (27.9)	84.4 (25.4)
Mental Health	76.7 (16.6)	74.4 (16.3)
Health Perceptions	52.8 (24.4)	49.2 (23.6)
Pain	41.6 (27.0)	47.6 (21.3)

Data are mean (SD). T2D: Type 2 diabetes; BMI: Body mass index; GGT: Gamma-glutamyl transferase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein

At 12-weeks, 35.7% of participants in the Pharm-TCR group were completely off all glucose-lowering medications compared to 0% in the TAU group (absolute difference = 35.7%, 95% CI 25.9 to 44.8%,  $p<0.0001$ ). Within the Pharm-TCR group, 17.3% of participants achieved a HbA1c of  $<6.5\%$  (i.e., below the diagnostic threshold for diabetes diagnosis) and were not taking any glucose-lowering medications compared to 0% in the TAU group (absolute difference = 17.3%, 95% CI 9.7 to 24.7%,  $p<0.0001$ ). Exploratory subgroup analyses for the primary endpoint of no medications by sex and insulin user status are presented in Supplementary Table 1. Changes in glucose lowering medications and blood pressure lowering medications, separated by medication class, are displayed in Supplementary Tables 3 and 4, respectively. To compliment the binary primary outcome, the Pharm-TCR group had lower mean medication effect score (MES) at 12 weeks ( $p<0.0001$ ; Table 2). Weekly MES in the Pharm-TCR group is displayed in Figure 2.

Pharm-TCR led to improvements in cardiometabolic health, anthropometrics, and health-related quality of life (HrQL)

Secondary outcomes are reported in Table 2. Among clinical blood markers, HbA1c, fasting glucose, triglycerides, and GGT at 12 weeks were all lower in the Pharm-TCR versus TAU group (all  $p<0.0001$ ). Mean body weight, body mass index (BMI), waist circumference, body fat percentage, and systolic and diastolic blood pressure were also lower at 12 weeks in the Pharm-TCR group when compared to TAU (all  $p<0.0001$ ). For measures of HrQL, role functioning,

mental health, health perceptions, and pain all improved in the Pharm-TCR group versus TAU ( $p<0.05$ ). Descriptive outcomes assessed weekly in the Pharm-TCR group are displayed in Figure 2. Mean daily macronutrient and kilocalorie intake at baseline, week 6, and week 12 are reported in Supplementary Table 5.

The exploratory statistical mediation analysis for the HbA1c (%) outcome revealed an indirect treatment effect (mediated via the change in body mass) of -0.8 (95% confidence interval: -1.3 to -0.3) percentage points ( $P=0.001$ ). This mediation effect represents 57% of the total causal effect of -1.4 percentage points (Table 2). The direct effect (not mediated by the change in body mass) was -0.6 (-1.2 to -0.04) percentage points ( $P=0.037$ ).

#### Adverse events

There were four adverse events reported in the Pharm-TCR group and no adverse events reported in the TAU group. Two of the adverse events were related to mild hypoglycemic events (recorded blood glucose levels of 4.1 mmol/L and 3.5 mmol/L); both events occurred when participants were reluctant to reduce insulin dosages by the recommended amount (one at the instruction of their endocrinologist) and were treated by the participants by consuming carbohydrates upon advice of their pharmacist. Upon following the recommended medication adjustments, these participants reported no more hypoglycemic symptoms. One adverse event was related to reporting hypoglycemic symptoms; however, the participant recorded blood glucose values no lower than 5.2 mmol/L. The cause of these symptoms was suggested to waiting too long between meals. Upon resolution of this issue, all hypoglycemic symptoms



139 stopped. The final adverse event was a cardiac event that occurred three weeks into the study and  
 140 was deemed not related to the intervention by the data safety monitoring board.

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Table 2: Secondary outcomes measured at 12-week follow-up

	Pharm-TCR	TAU	Treatment Effect	p value
Body weight (kg)	91.9	103.9	-12.0 (-13.6 to -10.4)	<0.0001
BMI (kg/m <sup>2</sup> )	31.2	35.6	-4.4 (-5.0 to -3.7)	<0.0001
Waist Circumference (cm)	102.4	113.8	-11.4 (-13.1 to -9.7)	<0.0001
Body Fat %	35.0	38.6	-3.7 (-5.0 to -2.5)	<0.0001
Systolic Blood Pressure (mmHg)	124	137	-13 (-17 to -8)	<0.0001
Diastolic Blood Pressure (mmHg)	75	83	-9 (-12 to -5)	<0.0001
HbA1c (%; percentage points)	6.4	7.8	-1.4 (-1.8 to -1.0)	<0.0001
HbA1c mmol/mol	46	61	-15 (-20 to -11)	<0.0001
Fasting Glucose (mmol/L)	7.2	9.1	-2.0 (-2.9 to -1.1)	<0.0001
GGT (mmol/L)	19.5	26.9	-27.6 (-38.5 to -14.7)% <sup>#</sup>	0.00016
AST (mmol/L)	20.6	20.5	0.9 (-11.3 to 14.9)% <sup>#</sup>	0.89
ALT (mmol/L)	24.7	26.0	-5.0 (-19.7 to 12.6)% <sup>#</sup>	0.55
HDL (mmol/L)	1.24	1.18	0.05 (-0.01 to 0.12)	0.13
LDL (mmol/L)	2.42	2.24	0.17 (-0.04 to 0.38)	0.106
Total Cholesterol (mmol/L)	4.14	4.22	-0.07 (-0.36 to 0.19)	0.60
Triglycerides (mmol/L)	1.00	1.49	-34.3 (-43.4 to -23.7)% <sup>#</sup>	<0.0001
CRP (mmol/L)	3.0	3.5	-12.4 (-30.3 to 10.2)% <sup>#</sup>	0.26
Medication Effect Score	0.6	2.2	-1.6 (-2.0 to -1.2) <sup>†</sup>	NA <sup>†</sup>
Leisure Score Index	30.5	25.4	5.1 (-4.3 to 15.3) <sup>†</sup>	NA <sup>†</sup>
Health Related Quality of Life				
Physical Functioning	72.5	71.8	0.7 (-7.7 to 9.9) <sup>†</sup>	NA <sup>†</sup>
Role Functioning	88.6	75.0	13.6 (2.4 to 26.3) <sup>†</sup>	NA <sup>†</sup>
Social Functioning	93.8	87.8	6.1 (-2 to 14.3) <sup>†</sup>	NA <sup>†</sup>
Mental Health	83.4	76.5	6.9 (1.9 to 12.7) <sup>†</sup>	NA <sup>†</sup>
Health Perceptions	70.6	51.4	19.2 (13.2 to 25.4)	<0.0001
Pain	28.5	36.0	-7.5 (-17.2 to -0.1) <sup>†</sup>	NA

Data are adjusted means (Pharm-TCR & TAU) and effect estimates (Treatment Effect) and 95% confidence intervals derived from constrained baseline longitudinal analysis via linear mixed models. P-values are from two-sided tests. Secondary outcome p-values were not adjusted for multiple comparisons. <sup>†</sup> bias-corrected and accelerated confidence intervals derived from non-parametric bootstrap analysis. <sup>#</sup> Treatment effect expressed as a percent difference (ratio of geometric means) from log-transformed analyses (Pharm-TCR vs. TAU). 'NA', a precise P value cannot be obtained for a BCa bootstrap analysis. T2D: Type 2 diabetes; BMI: Body mass index; GGT: Gamma-glutamyl transferase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein.

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## 145 Discussion

146 There is mounting evidence that type 2 diabetes can be reversed through nutritional  
147 interventions. What must be considered now is how people with type 2 diabetes can access  
148 efficacious interventions and how healthcare practitioners can safely deploy them. This study  
149 provides RCT level evidence that community-based pharmacists can effectively and safely  
150 implement a dietary intervention that rapidly reduces need for glucose-lowering medications and  
151 improves cardiometabolic health in people with type 2 diabetes within a real-world setting.

152

153 When treating type 2 diabetes, standard clinical practice is to target glucose control and key risk  
154 factors that are associated with the development of micro- and macrovascular disease<sup>13</sup>.  
155 Cardiovascular disease accounts for ~33-50% of all diabetes related deaths<sup>14</sup>. In this study, we  
156 demonstrate rapid improvements in glycemic control (while glucose-lowering medications were  
157 withdrawn or reduced), body weight, waist circumference, triglycerides, and blood pressure  
158 following the Pharm-TCR intervention. Furthermore, we report a significant reduction in GGT  
159 levels, which is correlated to reductions in excess liver fat<sup>15</sup>. Given that excess liver fat is linked  
160 with liver insulin resistance<sup>15</sup>, and therefore elevated fasting glucose levels, it is unsurprising that  
161 fasting glucose was substantially reduced in the Pharm-TCR group. Taken together, these data  
162 could indicate a depletion of harmful liver fat and a shift toward improved overall metabolic  
163 control. Interestingly, the sizeable reductions in blood pressure occurred despite reduced blood  
164 pressure medication usage in the Pharm-TCR group. The systolic blood pressure reductions in

the Pharm-TCR group equate to a ~25% reduction in total cardiovascular mortality risk<sup>16</sup>. Post-intervention Pharm-TCR triglyceride levels and the reductions in body weight and waist circumference have also been linked to meaningful reductions in cardiovascular risk<sup>17–19</sup>. When combined with the significant reductions in glycemia, the Pharm-TCR intervention elicited widespread improvements that would be expected to markedly reduce risk for both micro- and macrovascular diseases. Several HrQL variables also improved following the Pharm-TCR intervention, providing evidence of enhanced quality of life. Collectively, these broad health improvements indicate that the Pharm-TCR intervention is treating the disease rather than just managing the resulting hyperglycemia. If these improvements are sustained over time, a reduction in risk for common co-morbidities of type 2 diabetes would be expected.

Medication changes in clinical trials of similar nutritional interventions (i.e., combined low-carbohydrate, energy-restricted diets) in T2D are often not reported in great detail; however, Goday et al.<sup>20</sup> and Morris et al.<sup>21</sup> do report a reduction in medication use as descriptive or exploratory outcomes. The cardiometabolic health improvements observed in our trial are in line with HbA1c, weight loss, and changes in lipids in a study led by primary care nurses<sup>21</sup> and physicians<sup>20</sup>. Taken together, our findings suggest similar efficacy for treatment outcomes in low-carbohydrate, energy-restricted nutritional interventions implemented in community pharmacies.

The exploratory statistical mediation analysis for the HbA1c outcome showed that over half of the total mean treatment effect was mediated by the change in body mass. Gummesson et al.<sup>22</sup> reported a linear ‘dose-dependent’ relationship between weight loss and HbA1c reduction, with

an estimated mean HbA1c reduction of 0.1 percentage points for each 1 kg of weight loss. In the current trial, the mean weight loss was approximately 12 kg, which suggests a mean reduction in HbA1c of around 1.2 percentage points - close to our observed point estimate of 1.4 percentage points. Nevertheless, only 57% of the mean reduction in HbA1c was mediated by weight loss in our trial. The direct effect of the intervention (not mediated by weight loss) could be due, in part, to carbohydrate restriction *per se*<sup>23</sup> although other aspects of glucoregulation (e.g., insulin sensitivity, beta-cell function) could be involved.

A specific strength of this study was the use of pharmacists to deliver the nutritional intervention in the community. The need for rapid medication adjustments (i.e., within days/weeks to avoid predictable medication related events) when following a low-carbohydrate, low-calorie diet necessitates that someone knowledgeable in both type 2 diabetes and medication management has frequent and direct contact with participants. Given the risk of hypoglycemia and hypotension in this scenario, as well as the frequent visits that people with type 2 diabetes typically make to their local pharmacy<sup>9</sup>, community pharmacists were uniquely positioned to fill this role. Although the intention was not for pharmacists to replace dietitians in delivering nutrition therapy, they were a suitable choice given the commercial weight loss plan that was selected to standardize the delivery of the nutritional intervention. This study highlights the potential of pharmacists in a multidisciplinary health team strategy that includes nutrition therapy. Given the current burden on primary care physicians in many countries, the lack of access to registered dietitians, and the fact that people with diabetes typically make 50% more visits to their pharmacists than their primary care physicians<sup>9</sup>, future studies should investigate how a pharmacist-supported care model can be more broadly implemented.

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212 Recently, studies have reported type 2 diabetes remission as an outcome<sup>6,24</sup>; however, the criteria  
213 used to define remission are often inconsistent between studies<sup>25</sup>. The American Diabetes  
214 Association<sup>26</sup> has previously suggested criteria for type 2 diabetes remission that was based  
215 primarily on results of bariatric surgery studies. These criteria include the important caveat that  
216 remission of diabetes must demonstrate sustained improvements in glycemia in the absence of  
217 medications or ongoing therapy for at least one year. While a group of participants in this study  
218 did achieve normoglycemia while not taking glucose-lowering medications, the study's  
219 relatively short duration precludes defining this as type 2 diabetes remission. Recently, Taylor<sup>27</sup>  
220 used the term post-diabetes to describe individuals who had achieved sub-type 2 diabetes  
221 glycemic levels and ceased using glucose-lowering medications. This is fitting as it implies the  
222 person is no longer in a state of type 2 diabetes but may be at increased risk to redevelop type 2  
223 diabetes due to potentially irreversible pathophysiological alterations that may have already  
224 occurred. The terms remission and reversal both imply that the pathophysiological alterations  
225 contributing to type 2 diabetes (i.e., beta-cell dysfunction and insulin resistance) have improved.  
226 Consequently, without directly measuring these parameters it would be impossible to use these  
227 terms. For this reason, we have chosen not to use these terms to describe our results. Whether the  
228 numerous beneficial improvements in cardiometabolic health observed with the Pharm-TCR  
229 intervention constitute type 2 diabetes reversal, type 2 diabetes remission, or classification of  
230 post-diabetes will require further study.

231

232 Although relatively short-term in duration, there are specific strengths of the study that should be  
233 highlighted. The trial was designed to be pragmatic in nature to allow for insights that could be

beneficial for the implementation of similar interventions in the community. As such, having community pharmacists deliver the intervention in a RCT design is a major strength of the study. Furthermore, using a standardized medication deprescription plan allowed for consistent implementation of the Pharm-TCR intervention in a safe and scalable manner.

Whilst not unexpected, participant attrition was a limitation to this study. Regardless, we treated dropouts in both groups as not achieving the primary outcome, so we feel the estimate of the effect of the intervention is robust. Furthermore, exploratory subgroup analyses suggested that the mean effect of the intervention was not substantially different between men and women, or insulin users versus non-users. However, we caution that confidence intervals for these subgroup effects are wide, as the trial was not powered for sub-group interactions. Finally, for continuous secondary outcomes we utilized a constrained baseline longitudinal analysis via a linear mixed model<sup>28</sup>. When there are no missing data, this model is equivalent to a standard regression model with baseline included as a covariate (ANCOVA). With missing data, the constrained baseline model is superior, as all participants with at least one measurement (baseline or post-intervention) are included in the analysis, given that baseline is part of the outcome vector. Thus, while we do not believe that the loss to follow-up negatively impacted the robustness of our results, we acknowledge that the attrition rate indicates that this type of intensive intervention delivered in the community, even while closely supported, might not be suitable for everyone.

Although this trial was designed to compare the Pharm-TCR intervention to usual care (i.e., TAU), some aspects of the design should be emphasized to ensure proper interpretation of the

findings. The Pharm-TCR intervention was given to participants free of charge. It is possible that this could impact the translation of the results. Furthermore, although a comparison of cost-savings via medication use reduction vs. the cost to implement the intervention is an important question to be answered in future research, this study was not designed for a cost-effectiveness analysis. Participants in the Pharm-TCR intervention also received more contact with the study personnel than participants in the TAU group. As the trial design was pragmatic in nature, the aim was to compare the Pharm-TCR intervention (which includes both the diet aspect and the increased monitoring) to usual care. As such, the outcomes in the Pharm-TCR group cannot be attributed entirely to the effects of the diet alone.

For a patient with type 2 diabetes, undertaking an impactful dietary change can be potentially dangerous if not properly informed and/or monitored by qualified healthcare personnel. The results of this study suggest that pharmacists can fill this role and can help to safely deprescribe glucose-lowering medications. Future research should investigate the durability of the cardiometabolic improvements observed and explore ways to optimize delivery of therapeutic nutrition by incorporating community pharmacists into type 2 diabetes care teams.

The community pharmacist-led therapeutic carbohydrate- and energy-restricted dietary intervention effectively improved cardiometabolic health outcomes while safely reducing or eliminating glucose-lowering medications in patients with type 2 diabetes. Pharmacists could be viewed as an accessible and innovative option for implementing community-based and nutritional interventions for people with type 2 diabetes.

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## 280 Methods

### 281 Study Design and Participants

282 A pragmatic community-based RCT following a parallel-group design was conducted through 12  
283 community pharmacies (independently owned within the same pharmacy banner) throughout  
284 southern British Columbia, Canada. Ethics approval was granted by UBC Clinical Research  
285 Ethics Board (H16-01539) and written informed consent was obtained from all study participants  
286 prior to enrollment. Study conduct was performed in accordance with the ethical principles  
287 outlined in the World Medical Association Declaration of Helsinki. The trial was registered on  
288 ClinicalTrials.gov (NCT03181165) on June 8<sup>th</sup>, 2017 and the protocol detailing participant  
289 recruitment, study conduct, and planned data analyses is published elsewhere<sup>12</sup>.

290

### 291 Randomization and Blinding

292 Participants were randomized to either the pharmacist-led, therapeutic carbohydrate-restricted or  
293 treatment-as-usual control groups for 12 weeks. Randomization was performed by the  
294 pharmacist at each site through a secure password-protected website maintained by the Centre  
295 for Health Evaluation and Outcome Sciences (CHEOS). Random allocation was stratified by site  
296 (pharmacy) and glucose-lowering medications ( $\leq 2$  vs.  $\geq 3$  or taking exogenous insulin) and  
297 performed on a 1:1 ratio using variable permuted block sizes. Allocation lists were prepared  
298 using computer generation at CHEOS by a statistician unassociated with the study. Due to the  
299 nature of the trial, it was not possible to blind participants, study personnel at pharmacies, or  
300 research assistants to group allocation. The statistical analysis was also performed unblinded.



301

302 Participant inclusion criteria were: ability to provide written informed consent, age 30-75 years,  
303 type 2 diabetes diagnosis by a physician, using at least one glucose-lowering medication, and a  
304 body mass index of  $\geq 30 \text{ kg}\cdot\text{m}^2$ . Exclusion criteria included: history of a heart attack in the last  
305 two years; current unstable cardiovascular disorder; history of liver disease, kidney disease or  
306 impaired renal function; currently pregnant, lactating or planning to become pregnant within the  
307 next 12 months; diagnosed neurological disorder; history of bariatric surgery; history of cancer  
308 within the last five years; or dietary restrictions that would inhibit adherence to the intervention  
309 diet.

310

#### 311 Study Procedures

312 Potentially eligible participants were invited to the nearest participating pharmacy to review the  
313 eligibility criteria and study consent form. Recruitment was performed via a combination of  
314 newspaper and online advertising, posters posted in pharmacies, and by word of mouth in each  
315 respective study site location. Prior to any data collection, written informed consent was obtained  
316 and participants' primary care physicians were notified of their participation. Upon admittance,  
317 eligible participants underwent baseline assessment of medication use, anthropometrics, blood  
318 pressure, and completed study questionnaires measuring HrQL and habitual physical activity  
319 (Godin Leisure-Time Exercise Questionnaire) at the pharmacy. A fasting blood sample was  
320 obtained by a local laboratory and participants completed a 3-day diet record to assess habitual  
321 food intake.

Participants in the Pharm-TCR group were asked to follow a commercial weight loss diet plan (Ideal Protein) supplemented with whole foods. The diet plan was provided free-of-charge and utilized a variety of low-carbohydrate, energy-restricted, adequate-protein meals and snacks that were used in combination with select meats and vegetables. Based on individualized food choices selected from within the diet plan, the daily macronutrient content equated to <50g carbohydrates, ~35-45g fat, and ~110-120g protein for a total of ~850-1100 kcal. Participants in the Pharm-TCR group had weekly visits to the pharmacy to meet with a lifestyle coach and pharmacist to monitor progress, collect intervention foods, and assess medication usage. Lifestyle coaches managed scheduling and administrative tasks and were responsible for collecting anthropometric and blood pressure data while the pharmacists were responsible for all disease and medication data collection, information, and decisions. The medication deprescription plan is outlined in the supplementary information of the published protocol paper<sup>12</sup> (<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3873-7#Sec18>). Data collected at weekly visits included: weight, height (visit 1 only), BMI, waist circumference, body fat % (bioelectrical impedance analysis), blood pressure, capillary blood ketones, and medication usage. On week 6 of the diet, participants completed another 3-day diet record. On the final visit, in addition to the typical weekly assessments, participants were assessed for the same blood, HrQL, diet record, and habitual physical activity measures that were collected at baseline.

Participants in the TAU group were given standard medication advice by their pharmacist as well as information pamphlets on diet and lifestyle conforming with 2013 Diabetes Canada (formerly the Canadian Diabetes Association) Clinical Practice Guidelines. Participants in the TAU group did not attend weekly meetings during the 12-week control period; however, they completed a 3-

day diet record on week 6, similar to the Pharm-TCR group. Following the 12-week period, TAU participants returned to the pharmacy where they were assessed for the same blood, anthropometrics, HrQL, diet record, and habitual physical activity measures that were collected at baseline. Participants allocated to the TAU group were given the option of receiving the Pharm-TCR intervention after their initial 12-week TAU period in an effort to retain participants.

## Outcome measures

The primary outcome measure was a binary outcome of either using or not using glucose-lowering medications after the 12-week study period. Secondary outcomes assessed at baseline and 12 weeks included HbA1c, change in glucose lowering medication dose, BMI, body weight, waist circumference, body fat percentage, HrQL, blood lipid profile (total, HDL & LDL cholesterol, triglycerides), liver function tests (ALT, AST, and GGT), fasting plasma glucose, blood pressure, change in blood pressure medication dose, and a binary outcome of achieving both HbA1c < 6.5% and no glucose-lowering medication use. Body weight and body fat percentage were assessed using the Tanita model DF-430 U (IL, USA), blood pressure was assessed using the PharmaSmart Model PS-2000C (BC, Canada), height was measured using the Seca model 700 (Germany), and waist circumference was assessed by measuring the distance around the waist at the top of the iliac crest with a tape measure. HbA1c, fasting plasma glucose, blood lipid profile, and liver function tests were analyzed by provincially-accredited laboratories per standard clinical practice. Leisure score index was calculated by multiplying the number of strenuous, moderate, and mild bouts of physical activity by 9, 5, and 2, respectively<sup>29</sup>. HrQL was assessed using the 20-item Medical Outcomes Study Short Form (SF-20) and analyzed as described in Stewart et al<sup>30</sup>. Medication effect score was calculated<sup>31</sup> as a continuous secondary

outcome to quantify changes in medication use that were not captured by the primary outcome. Briefly, MES reflects the overall intensity of a diabetes medication regimen and is based on medication dosages and their efficacy for reducing blood glucose. Secondary outcomes assessed during the weekly visits in the Pharm-TCR group were MES, BMI, waist circumference, body fat percentage, systolic blood pressure, and diastolic blood pressure. Descriptive data for macronutrient content and energy intake from the 3-day food records were analyzed with MyFitnessPal (Under Armour®, Inc.).

## Statistical Analysis

All analyses were performed using R<sup>32</sup> and Stata software<sup>33</sup>. Data were analyzed as randomized. For the primary outcome, any participants lost to follow-up were presumed to be still using glucose-lowering medications. In Stata software, we applied a generalised linear model with a binomial distribution and logit link, with the Huber/White/sandwich variance estimator. To permit convergence, given zero events in the TAU arm, we specified the ‘asis’ command. The difference in proportion (Pharm-TCR vs. TAU) achieving ‘no medications’ and its asymmetric 95% confidence interval was derived using the -regpar- program<sup>34</sup>. The binary secondary outcome (both HbA1c <6.5% *and* ‘no medications’) was analysed with the same model. Exploratory subgroup analyses by sex and insulin user (yes/ no) were conducted by specifying a subgroup\*treatment interaction. The exploratory subgroup analyses for the primary outcome and the secondary outcomes of continuous HbA1c and body weight (by sex) are included in Supplementary Tables 1 and 2.

For the continuous secondary outcomes, missing data were assumed to be missing at random. Data were analyzed using constrained baseline longitudinal analysis via a linear mixed model<sup>28</sup>, which allows all participants with at least one measurement (baseline or post-intervention) to be included in the analysis as baseline is part of the outcome vector. The lme4 package<sup>35</sup> was used specifying Satterthwaite degrees of freedom, with fixed effects for timepoint (Pre vs. Post 12-weeks), treatment, sex, and the stratified allocation factors - study site and glucose-lowering medication use [2 or less, 3 or greater or taking exogenous insulin]) - and a random effect for participant to account for repeated measures within participants. 'Treatment' is a factor coded '1' if time = post and group = Pharm-TCR and coded zero otherwise. Subgroup analysis by sex was conducted for HbA1c and body weight by adding a sex\*treatment interaction term. For descriptive purposes, outcomes assessed at the weekly visits in the Pharm-TCR group were analyzed using a linear mixed model with fixed effects for week (0 to 12), sex, and the stratification factors (as above), and a random effect for participant.

Model specification was assessed visually using normal probability plots and residuals vs. fitted values plots. When the behaviour of the model residuals warranted a log transformation, effect estimates and 95% confidence intervals were back-transformed to ratio (percentage) differences using the emmeans package<sup>36</sup>. In cases where a log transformation could not be used (e.g. due to zero values), nonparametric bootstrap analyses were performed with 2000 resamples with replacement, and bias corrected and accelerated 95% confidence intervals were calculated with the boot package<sup>37,38</sup>.

We conducted an exploratory statistical mediation analysis using the Stata -sem- module, to examine the extent to which the observed treatment effect on HbA1c was mediated by the change in body mass. This analysis partitions the total causal effect into direct and indirect effects. The indirect effect is that passing through the putative mediator (change in body mass). The indirect effect/ total effect  $\times 100$  gives the proportion (%) of the total treatment effect mediated by the change in body mass.

A sample size of approximately 100 per group was required to provide 80% power to detect a 20% difference (odds ratio of 2.67) in the proportion of patients on zero glucose-lowering medications (assuming 20% in TAU), with a two-sided P value of 0.05<sup>39</sup>. Throughout, 95% confidence intervals are interpreted as the plausible range of effect sizes compatible with the data and model.

#### Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing.

#### Author Contributions

The principal investigator JPL, and head pharmacist SM conceived the study and designed the intervention. JPL, SM, and CD performed the literature search prior to the study design. JPL, SM, JS, AMB, and CD contributed to the study design. SM, CD, JDJ, and JW were involved in data collection, CD oversaw day-to-day conduct of the study with support from JPL and SM. JW

provided physician support. AMB, JS, CD, and KG performed the data analysis and statistical analysis. The underlying data were verified by CD and JPL. Figures and tables were created by CD. JPL, JDJ, AMB, and CD were involved in interpretation of the data. The first draft of the manuscript was written by CD with guidance from JPL. All authors reviewed the manuscript, revised it critically for important intellectual content, and approved the final version.

#### Competing Interests Statement

JPL holds founder shares and advises for Metabolic Insights Inc., and is volunteer Chief Scientific Officer for the not-for-profit Institute for Personalized Therapeutic Nutrition. SM is employed as Chief Executive Officer for the not-for-profit Institute for Personalized Therapeutic Nutrition. JW is a member of the Scientific Advisory Board, and has received travel support and speaker's honoraria, from Atkins Nutritionals Inc. JDJ is Chair of the Board for the Institute for Personalized Therapeutic Nutrition and receives no compensation. CD, JS, AMB, and KG have nothing to declare.

#### Data Availability

At the time of consent, it was not explicitly stated that data would be freely available in a public repository. As such, the corresponding author (JPL) is the custodian of the data and will provide access to deidentified and processed participant data for academic purposes on request ([jonathan.little@ubc.ca](mailto:jonathan.little@ubc.ca)), with the completion of a data access agreement. Source data for Figure 2 are provided as a Source Data file.

456 Code Availability

457 Code used for statistical analyses is available at DOI 10.17605/OSF.IO/76N28.

458

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Figure 1: Trial CONSORT flow diagram. Pharm-TCR: Pharmacist-led therapeutic carbohydrate restriction; TAU: Treatment-as-usual; ITT: Intention-to-treat. Created with BioRender.com.

Figure 2: Data are weekly effect estimates for changes from baseline (Week 0; gray line) with confidence intervals in the Pharm-TCR group for a) medication effect score (MES); b) body mass index; c) waist circumference; d) body fat percentage; e) systolic blood pressure; and f) diastolic blood pressure. Values are effect estimates for adjusted mean change from baseline in a-f. Bias-adjusted and accelerated confidence intervals derived from non-parametric bootstrap analysis are presented in panel a. Error bars for panels b-f represent 95% confidence intervals. Data are based on participants for which baseline data were collected (n=92) except for waist circumference (n=90) and body fat percentage (n=91). Source data are provided as a source data file.



